REMARKS

The present invention relates to compositions and methods for use in the diagnosis of subclinical atherosclerosis.

Despite advances in treating coronary heart disease (CHD), a large number of CHD victims die suddenly without prior symptoms. A recent consensus document suggests that available screening and diagnostic methods are insufficient to identify high-risk CHD patients before the first event occurs, and calls for screening of all asymptomatic men 45-75 years of age and asymptomatic women 55-75 years of age in order to detect and treat those with subclinical atherosclerosis. *Am. J. Cardiol.* 98:2H-15H, 2006.

The present invention relates to methods and compositions for identifying subjects at an increased risk for subclinical atherosclerosis. These methods comprise performing an assay that detects monocyte chemoattractant protein-1 ("MCP-1") in a sample from the subject, and correlating the results of that assay to the subject's risk of subclinical atherosclerosis. In various dependent claims, the methods can further comprise the use of one or more additional risk factors in combination with the MCP-1 assay result to assess the subject's risk.

The specification has been amended to insert a Sequence Listing and to add a Sequence Listing identifier to the specification. The amendments raise no issue of new matter.

The claims have not been amended. Applicants respectfully request reconsideration of the claimed invention in view of the following remarks.

1. Sequence Listing

A Sequence Listing paper copy has been provided herewith along with a certification. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

2. 35 U.S.C. §112, First Paragraph (written description)

Applicants respectfully traverse the rejection of claims 40 and 41 as allegedly failing to satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

Independent claim 32 reads as follows, with all other claims depending from this claim:

> A method of identifying an increased risk of subclinical atherosclerosis in a human subject, comprising
>
> performing an assay that detects monocyte chemoattractant protein-1 on a blood sample from said subject to provide a monocyte chemoattractant protein-1 assay result; and
>
> correlating the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject.

Claims 40 and 41 depend from, and so contain all of the limitations of claim 32, which is not subject to this rejection. The rejected claims read as follows:

> 40. A method according to claim 32, further comprising performing an assay that detects one or more other subject-derived markers in said sample to provide one or more additional assay results, and said correlating step comprises correlating the monocyte chemoattractant protein-1 assay result and said one or more additional assay results to the risk of the presence or absence of subclinical atherosclerosis in the subject.
>
> 41. A method according to claim 40, wherein said one or more other subject-derived markers are independently selected from the group consisting of specific markers of myocardial injury, specific markers of neural tissue injury, markers related to blood pressure regulation, markers related to coagulation and hemostasis, markers related to inflammation, and markers related to apoptosis.

Thus, these claims cover the possibility that MCP-1 is used in conjunction with one or more additional biomarkers in the method of claim 32. The Examiner takes the position that written description is lacking for claims 40 and 41 since "the claims are not limited as to the number of markers." Office Action, page 8.

The present claims are directed to risk stratification; that is, identifying an increased risk of subclinical atherosclerosis in a human subject. The present specification

demonstrates that elevations in MCP-1 levels indicate a significantly increased risk of subclinical atherosclerosis in a subject. Specification, Example 5. Applicants also note that Deo *et al., J. Am. Coll. Cardiol.* 44: 1812-18, 2004, published after the filing date of the present application, confirms the ability of MCP-1 to identify an increased risk of subclinical atherosclerosis in accordance with the present claims. Paragraph [0017] of the specification states that MCP-1 may be used in conjunction with one or more additional biomarkers in a "biomarker panel" approach. A number of preferred biomarkers which may be used in such methods are described in the following paragraphs in the specification.

While it is preferred that such additional biomarkers act synergistically with MCP-1 in such methods, one or more additional biomarkers could be combined with MCP-1 in the claimed invention and the value of MCP-1 would not be lessened, even if the other biomarkers added no further value to the risk stratification method.

But the specification also includes examples of biomarkers known in the art as markers of subclinical atherosclerosis. For example, CRP (discussed in paragraph [0007] of the specification) exhibits similar odds ratios for identifying subclinical atherosclerosis as those seen in the present study for MCP-1. Compare Wang *et al., Arterioscler. Thromb. Vasc. Biol.* 22: 1662-67, 2002, table 3, and paragraphs [0255] and [0256] of the present specification. Such blood-based tests can be used to screen for those individuals at increased risk for future cardiovascular events. Other biomarkers of subclinical atherosclerosis known from the literature include IL-6 (specification, paragraph [0144]), Soluble intercellular adhesion molecule-1 (*id.*, paragraph [0147]), and E-selectin (*id.*, paragraph [0177]). This list is by no means exhaustive.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* An adequate written description "may be shown by

any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a).

In the present case, the specification as filed adequately conveys to the skilled artisan that the inventor was in possession of the invention of claims 40 and 41 as of the filing date. Because the written description requirement demands no more, Applicants request that the rejections be reconsidered and withdrawn.

3. 35 U.S.C. § 112, first paragraph (enablement)

Applicant respectfully traverses the rejection of claims 32-36, 40, 41, 42, and 44 as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner's rejection appears to be premised on the assertion that because MCP-1 lacks specificity and so "does not satisfy features of indicator (risk marker/factor) for atherosclerosis, as MCP-1 is an indicator of a variety of diseases." Office Action, page 11. The Examiner also asserts that because only a subset of subjects having an elevated MCP-1 level have subclinical atherosclerosis, it "alone cannot be used as a specific indicator of atherosclerosis." Office Action, page 12. These assertions, however, are not in any way indicative of the understanding in the art.

Applicants note that Deo *et al., J. Am. Coll. Cardiol.* 44: 1812-18, 2004, published after the filing date of the present application, confirms the ability of MCP-1 to identify an increased risk of subclinical atherosclerosis in accordance with the present claims.

With regard to whether only "specific" markers can "satisfy features of indicator (risk marker/factor) for atherosclerosis," those of skill in the art understand that virtually all diagnostic tests lack the type of specificity the Examiner seems to believe is necessary. For example, D-dimer is not a "specific marker" of pulmonary embolism. *See, e.g.*, Indik and Alpert, *Prog. Cardiovasc. Dis.* 42: 261-272, 2000 (cited by the Examiner in the Office Action), page 262 ("Since D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis in the body, the

specificity of all DD assays is expected to be low"). Nevertheless, it is an FDA-approved test for use in the evaluation of pulmonary embolism, and so presumably does "satisfy features of indicator" for pulmonary embolism, the Examiner's opinion with regard to nonspecific tests notwithstanding.

Similarly, assays that detect BNP and NT-proBNP, and proBNP assays are FDA-approved for use in the diagnosis of heart failure. But, BNP is also FDA-approved as a risk marker in acute coronary syndromes. See, e.g., Triage® BNP Test package insert, page 1, section entitled "Intended Use." Likewise, elevated levels in the well known "prostate-specific antigen" ("PSA") test may be caused by conditions including prostate cancer, benign prostate enlargement, inflammation, and infection, and elevations are understood to be affected by both age and race. Despite the fact that only 25 to 30 percent of men who have a biopsy due to elevated PSA levels actually have prostate cancer, the PSA test is routinely used by artisans for initial diagnosis and screening. And CRP is a marker that is elevated in numerous inflammatory processes, including cancer, connective tissue disease, heart attack, infection, inflammatory bowel disease, lupus, pneumococcal pneumonia, rheumatoid arthritis, rheumatic fever, and tuberculosis. *See, e.g.*, http://www.nlm.nih.gov/medlineplus/ency/article/003356.htm. While only a fraction of subjects having an increased CRP level will have any one of these conditions, CRP tests are FDA approved and routinely used by clinicians.

While one might desire to have available "specific markers" for a particular disease or condition, that is typically not possible. Fortunately, even nonspecific markers can be useful clinically when in the hands of the skilled artisan, as the skilled artisan does not use such tests in an informational vacuum. Rather, diagnostic and prognostic tests are used by skilled medical personnel in concert with other available medical indicia related to a subject, and are not judged by the ability of a "specific marker" to give a definitive yes/no answer to the existence of a disease.

Moreover, the fact that not all patients might exhibit elevated MCP-1 levels, why this is of any relevance at all is unclear. Just as no biomarker is completely specific, no biomarker is completely sensitive. The present claims are directed to risk stratification; that is, identifying an increased risk of subclinical atherosclerosis in a human subject; and

the present specification demonstrates that elevations in MCP-1 levels indicate a significantly increased risk of subclinical atherosclerosis in a subject. Specification, Example 5. This fact is confirmed by the Deo *et al.* publication discussed above.

In addition, the Examiner refers to several publications in an attempt to paint the state of the prior art in a negative light. Many of these comments do not accurately represent the teachings of these publications. Furthermore, the publications cited by the Examiner represent a recitation of difficulties that *might* be encountered in practice in the general use of biomarkers, and concern how diagnostic methods might be shown to be ready for clinical application. As discussed hereinafter, neither is a sufficient basis for rejecting a claim under the enablement requirement.

The factors relevant to an enablement analysis are enumerated in *In re Wands*. Applicants attempt to address the Examiner's remarks in the context of the various *Wands* factors in the following remarks.

A. The nature of the invention

The present invention is related to the use of biomarker measurements to identify a subject's risk of subclinical atherosclerosis. In particular, independent claim 32 refers to:

> A method of identifying an increased risk of subclinical atherosclerosis in a human subject, comprising
>
> performing an assay that detects monocyte chemoattractant protein-1 on a blood sample from said subject to provide a monocyte chemoattractant protein-1 assay result; and
>
> correlating the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject.

Contrary to the Examiner's belief, nothing in this claim requires that a subject be definitively identified as suffering from subclinical atherosclerosis. The specification demonstrates that elevated MCP-1 is statistically associated with an increased risk of subclinical atherosclerosis, a fact confirmed by the Deo *et al.* publication. Because of this, a relative risk of subclinical atherosclerosis can be correlated to the level of MCP-1. That is all that the claimed method requires.

B. The state of the prior art

The state of the prior art is that biomarkers are routinely used in the art for diagnosis and prognosis of individual cardiac conditions.

With regard to traditional atherosclerosis risk factors, systolic blood pressure, blood glucose, and cigarette smoking had been reported as risk factors for subclinical atherosclerosis. Kuller et al., Am. J. Epidemiol. 139(12):1164-79, 1994. With regard to biochemical markers, CRP, LDL, and oxidized LDL had been reported to provide similar odds ratios as those seen in the present study for MCP-1. Wang *et al., Arterioscler. Thromb. Vasc. Biol.* 22: 1662-67, 2002, table 3. Hulthe and Fagerberg, *Arterioscler. Thromb. Vasc. Biol.* 22: 1162-67, 2002, abstract

Applicants also note that, since the present application was filed, Deo *et al., J. Am. Coll. Cardiol.* 44: 1812-18, 2004, reported on the use of MCP-1 in identifying an increased risk of subclinical atherosclerosis, as described in the present claims. Additionally, Beloqui *et al., Eur. Heart J.* 26:153-58, 2005, reported on the use of monocyte cyclooxygenase-2 activity; Nelson *et al., Am. J. Epidemiol.* 163:903-12, 2006, reported on the use of sphingomyelin; Amar *et al., J. Hypertens.* 24:1083-88, 2006, reported on the use of IL-6; and Orbe *et al., J. Thromb. Haemost.* 5: 91-7, 2007, reported on the use of matrix metalloproteinase-10; in each case as a risk marker for subclinical atherosclerosis. This list is exemplary only.

In contrast to the well established use of biomarkers in the art, the Examiner contends that MCP-1 lacks specificity and so "does not possess one of the important features of diagnostic markers as MCP-1... lacks specificity." Office Action, paragraph bridging pages 11 and 12. As discussed in some detail above, the Examiner's personal view of what is required to meet the enablement requirement in this regard does not square with the routine use of biomarkers in the prior art. Biomarker tests are routinely used to signal an increased or decrease probability of a particular diagnosis, particularly when used in concert with other available medical indicia, and any test (or even combination of tests) will have a level of sensitivity and specificity that typically does not meet the Examiner's "important feature" of 100% each.

If diagnostic tests needed to meet the standard that the Examiner applies – to be able to definitively identify the presence or absence of disease – both patients and physicians would be in dire straits indeed.

The Examiner also refers to several publications in an attempt to paint the state of the prior art in a negative light. Many of these comments amount to a recitation of difficulties that *might* be encountered in practice in the general use of biomarkers. That type of reasoning is not a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3. In addition, the Examiner's assertions about the limits of the prior art are not well founded.

The Examiner states that Bast *et al.*, *Clin. Cancer Res.* 11: 6103-8, 2005, "point to the 'lengthy process' of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically." Office Action, page 15. In addition to being merely a recitation of difficulties that *might* be encountered in practice, the Examiner has failed to acknowledge that this "lengthy process" quote, which is found on page 6105, right column, of Bast *et al.*, addresses why some marker tests do not obtain federal regulatory approval. It is not a requirement of the patent laws that a patent application be sufficient to obtain FDA approval, as considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. The reference to Bast *et al.* is nothing more than a personal opinion of the Examiner, unsupported by any evidence of record, that the claimed methods might not be ready for clinical application. This is not a basis on which to question the enablement of the claims. *See, e.g., Ex Parte Rollins and Stiles*, 2006 WL 2523796 at *5 ("at the risk of being repetitive, evidence that a claimed method was not ready for clinical application is not enough to show nonenablement. What is needed is evidence or sound scientific reasoning that undue experimentation would have been required to carry out the claimed methods).

The Examiner also states that LaBaer, *J. Proteome Res.* 4: 1053-9, 2005, "teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical

clinical test is even more daunting." Office Action, page 15. Again, this is nothing more than a recitation of difficulties that *might* be encountered in practice, and of basic considerations that the author believes should go into any biomarker discovery program. More appropriately, the LaBaer publication reflects considerations that are routine to one skilled in the field of biomarkers.

The Examiner further attempts to support the rejection (see page 15 of the Office Action) by reference to the following section from Baker, *Nature Biotechnology* 23: 297-304 (2005), page 298:

> Walking on Thin Ice
>
> 'Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is;' says Ole Vesterqvist, director of clinical discovery at NewYork-based Bristol-Myers Squibb. 'You start walking, and you get comfortable. Then you break through.' Vesterqvist describes an example in which published clinical data showed that people with heart failure had higher levels of the peptide endothelin I (ET-1) compared to healthy controls, based on immunoassays. But in studies at Bristol-Myers Squibb, these patients showed no increase in plasma concentration of the peptide, Eventually, Vesterqvist's group found research revealing that the previous studies used an antibody that cross-reacted with the precursor to ET-1, big-ET. Although levels of the precursor are higher in patients with heart failure, the levels of ET-1 are not. Ironically, the Bristol-Myers Squibb assay did not produce the expected results because it was more specific for ET-1 than assays previously used in other laboratories.

The discussion to which the Examiner refers is nothing more than an anecdotal report of a rather simple error on the part of one researcher in one example. To the extent the passage is meaningful at all, it speaks to the need for a rather basic understanding of the biomarker with which one is working.

Applicants respectfully submit that the state of the prior art is one of common usage of biomarkers generally, and that each of the publications cited by the Examiner are consistent with this understanding.

C. The relative level of skill in the art

The skill in the art is extremely high. The skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis and prognosis of patients, and also

has extensive experience in the generation and characterization of antibodies for use in such tests. As noted above with regard to the state of the art, the skilled artisan is well aware of the potential pitfalls that might be encountered in practice. The artisan is prepared to perform the necessary studies to practice the claimed methods, and understands that the required methods are routine in the art.

D. The quantity of experimentation necessary

The present claims do not relate to any new general methods for the analysis of biomarkers. Instead, the present invention lies in the discovery that elevations in MCP-1 levels indicate a significantly increased risk of subclinical atherosclerosis in a subject. Once MCP-1 has been identified, little is required of the skilled artisan in the way of experimentation to practice the invention.

In view of the teachings of the specification and the knowledge available in the art, the quantity of experimentation required to practice the invention is no more than routine. The specification provides the artisan with detailed examples of which markers to use and which cardiovascular disorders are to be distinguished. It further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis. When properly considered, it is apparent that what the Examiner likens to "tossing out the mere germ of an idea"(Office Action, page 18) is actually a complete description of how to make and use the claimed invention from start to finish.

E. The predictability of the art

In the present case, the methods to be followed are all routine; the only factor required to practice the claimed invention is the understanding that such methods should be pursued, an issue that is solved by reference to the present specification and claims.

The Examiner's comments in the Office Action regarding the state of the prior art (discussed above) are also relevant to an understanding of the predictability of the art. As discussed in detail above, assertions such as there can be a "lengthy process of assay development," that "many markers that correlate with disease statistically may not prove

to be useful clinically," or that "the process of converting such a biomarker into a practical clinical test" amount to broad allegations that the disclosure is speculative, coupled with a recitation of difficulties that *might* be encountered in practice. Such reasoning, however, is legally insufficient for rejecting a claim under the enablement requirement.

Applicants respectfully submit that the test of enablement is not whether certain scenarios may be constructed in which the invention might not work, but rather whether one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. The present specification and claims meet this standard.

F. The amount of direction or guidance

The specification provides the artisan with substantial guidance for the use of MCP-1 in identifying subjects that are at an increased risk of having subclinical atherosclerosis. The specification further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis.

G. The presence or absence of working examples

The specification provides exemplary data for the use of MCP-1 in the claimed invention, and demonstrates that elevated MCP-1 is statistically associated with an increased risk of subclinical atherosclerosis, a fact confirmed by the Deo *et al.* publication. Because of this, a relative risk of subclinical atherosclerosis can be assigned to a patient based on the level of MCP-1. The Examiner's belief to the contrary (Office Action, page 21: "the presence or amount of MCP-1 alone is not capable of specifically assessing the increased risk of atherosclerosis in a human subject") exhibits a failure to consider the data presented in the specification with the level of knowledge available in the art.

H. The breadth of the claims

The claims are circumscribed in their breadth, in that they refer to methods that comprise performing an assay that detects monocyte chemoattractant protein-1 on a

blood sample from a human subject to provide a monocyte chemoattractant protein-1 assay result; and correlates the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject, the Examiner's reference to the claims' "breadth" in the paragraph bridging pages 15 and 16 notwithstanding.

I. Conclusion

In the present case, the skilled artisan can, by simply following the extensive detailed guidance in the specification, perform the claimed methods using nothing more that routine experimentation. The rejection fails to consider the knowledge available in the art, being based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that *might* be encountered in practice. As such, the rejection does not present a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3.

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

4. 35 U.S.C. § 112, second paragraph (definiteness)

Applicants respectfully traverse the rejection of claims 33, 35, and 36 under 35 U.S.C. § 112, second paragraph, as allegedly failing to comply with the definiteness requirement.

Claimm 33, when including the limitations in claim 32 from which it depends, reads as follows:

> A method of identifying an increased risk of subclinical atherosclerosis in a human subject, comprising:
>
> performing an assay that detects monocyte chemoattractant protein-1 in a blood sample from said subject to provide a monocyte chemoattractant protein-1 assay result; and

> correlating the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject.
>
> wherein the assay step comprises determining the concentration of monocyte chemoattractant protein-1 in said sample, and
>
> the correlating step comprises comparing said concentration to a threshold concentration, wherein a concentration of monocyte chemoattractant protein-1 less than said threshold concentration is indicative of a first risk of subclinical atherosclerosis and a concentration of monocyte chemoattractant protein-1 greater than said threshold concentration is indicative of a second risk of subclinical atherosclerosis.

The Examiner states that the final clause of this claim renders the claim indefinite, as it is allegedly unclear if the "concentration of monocyte chemoattractant protein-1" referred to in the "correlating step" refers to the "concentration of monocyte chemoattractant protein-1" determined in the previous clause.

Applicants respectfully disagree. In fact, the final clause describes comparing the determined concentration to a threshold concentration, and clearly indicates how the comparison takes place: a concentration of monocyte chemoattractant protein-1 less than the threshold concentration is indicative of a first risk of subclinical atherosclerosis and a concentration of monocyte chemoattractant protein-1 greater than the threshold concentration is indicative of a second risk of subclinical atherosclerosis.

As the Board of Patent Appeals and Interferences recently pointed out, the Examiner must establish that a claim is insolubly ambiguous to establish indefiniteness:

> The threshold for indefiniteness is very high: the claim must be "insolubly ambiguous". . . . If one of skill in the art would understand the scope of the claim when read in light of the specification, then the claim complies with § 112(2). Claims need not be models of clarity. As long as the meaning is discernible, then even if construction is difficult and the result equivocal, the claim is nevertheless definite. Exxon Research & Eng'g Co., 265 F.3d at 1375, 60 USPQ2d at 1276; All Dental Prodx LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 779-80, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002) (no indefiniteness despite the lack of clarity).

Ex Parte Hicks, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.). Applicants respectfully submit that the claim language to which the Examiner refers cannot be considered insolubly ambiguous.

Because the claims do not rise to the level of being insolubly ambiguous, and are therefore definite within the meaning of 35 U.S.C. § 112, second paragraph, Applicants request that the rejection be reconsidered and withdrawn.

5. 35 U.S.C. §102

The Examiner has rejected claims 32, 33, 43 and 44 under 35 U.S.C. § 102(b) as allegedly being anticipated by Parthasarathy *et al.*, US20020052000 (hereinafter "Parthasarathy"). Applicant respectfully traverses this rejection.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also MPEP §2131.

The Examiner begins the anticipation analysis with the following statement: "[t]he instant claim recites "method of diagnosing atherosclerosis in a subject." Office Action, page 17. This is simply incorrect. The present claims recite "a method of identifying an increased risk of subclinical atherosclerosis in a human subject." By beginning with a fundamentally flawed interpretation of the claimed invention, the Examiner cannot establish a *prima facie* case of anticipation.

Parthasarathy discloses a method and kit "for the assessment of the state of lipid peroxidation of a host" and for "the identification and quantification of inflammatory disorders." *See, e.g.*, Parthasarathy, paragraphs [0013]-[0017] and [0020]. Concerning MCP-1, which is the subject of the present invention, Parthasarathy discloses that it is a "surrogate marker" of some unspecified inflammatory disease, of which "a cardiovascular disorder" is but one example. Parthasarathy, paragraphs [0097] and [0138]. It is also suggested that lipid peroxide forms of MCP-1 "may represent a sensitive and specific marker for lipid peroxide mediated vascular inflammatory events characteristic of atherosclerosis. Parthasarathy, paragraph [0098], emphasis added.

Importantly, Parthasarathy does not indicate that MCP-1 can be used to identify an increased risk of subclinical atherosclerosis, nor is there any exemplary data of any kind in Parthasarathy concerning detection of atherosclerosis at all. The claimed use of MCP-1 to aid in the early identification and treatment of those with subclinical atherosclerosis, demonstrated in the present specification in Example 5, is not disclosed in Parthasarathy.

Because Parthasarathy does not disclose each and every element of the present claims, Applicants respectfully submit that no *prima facie* case of anticipation has been established. Applicants, therefore, request that the rejection be reconsidered and withdrawn.

6. 35 U.S.C. §103

The Examiner has also rejected claim 34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Parthasarathy in view of Adelman *et al.*, U.S. Patent No. 5,482,935; claims 35 and 36 as allegedly being unpatentable over Parthasarathy in view of Duffus *et al.*, which defines the term "odds ratio"; and claims 40 and 41 as allegedly being unpatentable over Parthasarathy in view of Carville *et al., Clin. Chem.* 42: 1537-41, 1996. Applicant respectfully traverses these rejections.

Each of these rejections relies on Parthasarathy as the primary reference. But, as discussed above, the Examiner begins the analysis of the present claims with a fundamentally flawed interpretation of the claimed invention. By beginning with a fundamentally flawed interpretation of the claimed invention, the Examiner cannot establish a *prima facie* case of obviousness.

Moreover, the claimed invention, drawn to the use of MCP-1 in a method of identifying an increased risk of subclinical atherosclerosis in a human subject, is not disclosed in Parthasarathy. Parthasarathy discloses a non-limiting list of "surrogate markers," of which MCP-1 is but one marker, indicating that these are markers for some unspecified inflammatory disease, of which "a cardiovascular disorder" is but one example. Parthasarathy , paragraphs [0097] and [0138]. Parthasarathy suggests that lipid peroxide forms of MCP-1 and these other markers "may represent a sensitive and specific

marker for lipid peroxide mediated vascular inflammatory events characteristic of atherosclerosis." Parthasarathy, paragraph [0098], emphasis added. It requires a leap to extend this suggestion by modifying it to arrive at the claimed use of MCP-1 to identify an increased risk of subclinical atherosclerosis. Rejections on obviousness grounds must be based on some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006)). No such reasoning is provided by the Examiner in the present case.

None of the secondary references cure this flaw in the Examiner's analysis.

Adelman *et al.* is cited as allegedly disclosing that hyperlipidemia, hyperglycemia, diabetes, hypertension, obesity, cigarette smoking, familial hyperproteinemia, aging, and being male are risk factors for atherosclerosis.

Duffus *et al.*, is cited as a glossary which defines the term "odds ratio."

Carville *et al.* is cited as allegedly disclosing that acute myocardial infarction is associated with release of cardiac muscle proteins. It is noted here that the relationship of myocardial infarction to subclinical atherosclerosis is not discussed by the Examiner, and the skilled artisan would understand that the occurrence of an acute myocardial infarction is hardly a subclinical event.

Because the cited publications, considered alone or together, do not disclose or suggest each and every element of the claims, and because no motivation has been established to either combine or modify the cited publications to arrive at the claimed invention, Applicants brespectfully submit that no *prima facie* case of obviousness has been established. Applicants, therefore, request that the rejections be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the

undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 12/19/2007 By Barry Wilson

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Credit Card Authorization Confirmation Receipt

Client/Matter Number:	071949-5604
Client Name:	BIOSITE INCORPORATED FKA BIOSITE DIAGNOSTICS INC
Matter Description:	(US) MARKERS FOR DIFFERENTIAL DIAGNOSIS AND METHODS OF USE THEREOF - CIP
DenneMeyer ID:	071949-5604
Serial Number/ Case Information:	United States of America Patent Application 10/728067; USE OF THROMBUS PRECURSOR PROTEIN AND MONOCYTE CHEMOATTRACTANT PROTEIN AS DIAGNOSTIC AND PROGNOSTIC INDICATORS IN VASCULAR DISEASES;Kenneth F Buechler, Alan Maisel
Amount:	$1,050.00
Fee Description:	3MEOT
Credit Card #:	VISA 4715634889740050
Authorization Code:	525
Expiration Date:	11/30/2008
Name on Credit Card:	Barry S Wilson
Status:	Submitted

Transaction Code: ZTIHQU